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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/629,074	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9,11,12,17,19,21,22,25,30,32,33,40,42-50,52-56 and 58-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,17,19,21,22,25,30,40,44,45,48-50,52,53,56,58,59 and 62-65* is/are rejected.

7)☒ Claim(s) *11,12,32,33,42,43,46,47,54,55,60,61 and 66-71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed May 10, 2004 has been entered. Claims 1, 9, 11, 12, 17, 19, 22, 44, 52, and 58 have been amended. Claims 4, 6, 7, 8, 10, 18, 23, 26, 27, 29, 31, 38, 39, 41, 51, and 57 have been cancelled. Claims 63-71 have been newly added.

Accordingly, Claims 1-3, 9, 11, 12, 17, 19, 21, 22, 25, 30, 32, 33, 40, 42-50, 52-56, and 58-71 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 10, 2004 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 9, 17, 19, 21, 22, 25, 30, 40, 44, 45, 48-50, 52, 53, 56, 58, 59, and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,398,816 (Breitbart et al., filed September 4, 1997) and U.S. Patent No. 5,935,820 (Hu et al.).

Breitbart et al. disclose the use of genetically engineered cells expressing a number of specific bioactive molecules for bone repair. The claims specifically recite that "the cells are applied to or incorporated into a prosthesis for repair or replacement of bone, cartilage, or connective tissue" (see Claim 1). The claims further recite that the cells are genetically engineered to express an effective amount of growth factors "selected from the group consisting of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (FGF), insulin-like growth factor (IGF), endothelial derived growth supplement (EDGS), keratinocyte growth factor (KCF), osteogenin, skeletal growth factor (SGF), osteoblast-derived (BDGFs), retinoids, growth hormone (GH), bone morphogenic proteins (BMPs), and transferrin" (see Claim 5). Claim 9 is specifically directed to periosteal cells genetically engineered to express BMP-7. The specification explicitly points out that "TGF-beta enhances bone cell proliferation" (Column 6, line 56) and that TGF-β can be used to increase bone formation, promote fracture healing and induce bone growth around implants (Column 6, line 65 to Column 7, line 1). Claim 6 specifically recites the use of TGF-β. The specification discloses that genetically engineered periosteal cells are to be used for repair of bone (see abstract at lines 6-8). The specification further discloses that cells can be implanted directly into a defect in an amount effective to promote repair (Column 8, lines 38-39). The specification makes it clear that the invention covers cells transfected with more than one of the genes mentioned in the claims. For example, at Column 3, lines 41-43, the specification states that "for repair of bone, a gene **(or genes)** encoding bone morphogenic protein is transfected into periosteal cells." Furthermore, the claims recite "bioactive molecules" in the plural form. The specification discloses using adenoviral vectors to transduce the cells (Column 8, lines 8-10).

Hu et al. discloses that VEGF has four different forms of 121, 165, 189, and 206 amino acids due to alternative splicing (column 1, lines 52-56). The reference discloses that VEGF121 and VEGF165 are soluble and promote angiogenesis (column 1, lines 53-55) As early as 1992 it was known that VEGF is

responsible for persistent microvascular hyperpermeability to plasma proteins, a characteristic of normal wound healing (column 2, lines 8-14). Thus, VEGF was known to be an important factor in wound healing. Hu et al. further discloses a polynucleotide encoding VEGF2. The reference describes using the disclosed polynucleotide encoding VEGF2 "to promote growth of damaged bone and tissue" (Column 2, lines 38-42). At Column 9, lines 57-58, the reference discloses that VEGF2 may be used to induce the growth of damaged bone. Moreover, the reference specifically mentions using adenovirus to deliver a polynucleotide encoding VEGF2 (Column 10, lines 34-55). It discloses that cells may be transduced with the polynucleotide *ex vivo* (as recited in Claim 3 of the instant application) or *in vivo* (as recited in Claim 2 of the instant application).

Given that Breitbart et al. disclose the use of genetically engineered cells expressing a number of specific bioactive molecules for bone repair, including VEGF and TGF-β, and specifically points to using cells genetically engineered to express any VEGF, and further given that various VEGFs were known in the art, including VEGF121, VEGF165, VEGF189, and VEGF206, as evidenced by Hu et al., and further given that these were known to have similar properties, as discussed by Hu et al., and further given that Hu et al. specifically disclosed that one form of VEGF, VEGF2, is useful for promoting growth of damaged bone, the skilled artisan would have been motivated to use other VEGFs and polynucleotides encoding other VEGFs to promote growth of damaged bone. A reasonable expectation of success would have been anticipated because the various VEGFs known in the art were known to have similar biological properties, as discussed by Hu et al. Furthermore, in accordance with the guidance of Breitbart et al., the skilled artisan would have been motivated to use TGF-β in combination with the various VEGFs known in the art to promote growth of damaged bone.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 11, paragraph 3 of the response, Applicants assert that the '816 patent does not disclose or suggest the use of adenoviral vectors or bone grafts comprising a VEGF in combination with TGF-β1 to enhance bone growth or formation. On the contrary, the '816 patent explicitly suggests using adenoviral vectors (Column 8, lines 8-10), using TGF-β, which is merely an alternate name for TGF-β1 (as evidenced by the TGF-β1 entry in Online Mendelian Inheritance in Man, the OMIM database of Victor McKusick), using any VEGF, and using cells transfected with more than one of the genes mentioned in the claims, as discussed above. Hu et al. discloses the particular VEGFs known in the art at the time. In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller* 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.* 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claims 1-3, 9, 17, 19, 21, 22, 25, 30, 40, 44, 45, 48-50, 52, 53, 56, 58, 59, and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,525,030 (Eriksson, filed December 15, 1997), U.S. Patent No. 6,475,480 (Mehtali et al., filed July 6, 1999), and U.S. Patent No. 5,935,820 (Hu et al.).

Eriksson discloses a method for stimulating bone growth by repeatedly injecting expressible genetic material encoding a product that modulates bone growth into periosteal cells (see especially Claim 3). The specification discloses that a preferred gene for delivery can include a gene that encodes a product that can modulate bone growth, which products can include cytokines, particularly those listed in Table 3 (Column 16, line 66 to Column 18), including TGF-β. Many of the genes listed in Table 3 are also recited in Claim 2, including VEGF. Furthermore, it is noted that Claim 2 recites "and a combination of any of the foregoing." Such combinations would meet the limitations of the instant claims when

VEGF is included with TGF-β. The specification specifically states that a plurality of genes may be delivered in combination (Column 17, lines 4-5).

Mehtali et al. disclose an adenoviral vector which provides for improved expression of its cargo gene. The reference discloses a method for improving the expression and/or persistence of expression of a gene of interest in a mammal (see especially Claim 18).

Hu et al. discloses that VEGF has four different forms of 121, 165, 189, and 206 amino acids due to alternative splicing (column 1, lines 52-56). The reference discloses that VEGF121 and VEGF165 are soluble and promote angiogenesis (column 1, lines 53-55) As early as 1992 it was known that VEGF is responsible for persistent microvascular hyperpermeability to plasma proteins, a characteristic of normal wound healing (column 2, lines 8-14). Thus, VEGF was known to be an important factor in wound healing. Hu et al. further discloses a polynucleotide encoding VEGF2. The reference describes using the disclosed polynucleotide encoding VEGF2 "to promote growth of damaged bone and tissue" (Column 2, lines 38-42). At Column 9, lines 57-58, the reference discloses that VEGF2 may be used to induce the growth of damaged bone. Moreover, the reference specifically mentions using adenovirus to deliver a polynucleotide encoding VEGF2 (Column 10, lines 34-55). It discloses that cells may be transduced with the polynucleotide *ex vivo* (as recited in Claim 3 of the instant application) or *in vivo* (as recited in Claim 2 of the instant application).

Given that Eriksson discloses a method for stimulating bone growth by administering a gene to a periosteal cell and further given that Mehtali et al. discloses a method for improving the expression of a gene of interest in a mammal by using a specific type of adenoviral vector, one of skill in the art would have been motivated to employ the use of the adenoviral vector of Mehtali et al. in the method of Eriksson to boost the expression of the gene that will stimulate bone growth. Furthermore, given that Hu et al. discloses the various VEGFs known in the art at the time, the skilled artisan would have been able to use any of those VEGF-encoding polynucleotides in an adenoviral vector. Given that only standard

molecular biology techniques are required to prepare an adenoviral vector as taught by Mehtali et al. carrying any gene of interest, one of skill in the art would have anticipated a reasonable expectation of success for making the necessary adenoviral vectors and using them in the method disclosed by Eriksson.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 11, paragraph 6 of the response, Applicants assert that neither the '030 patent nor the '480 patent discloses or suggests the use of an adenoviral vector or bone graft comprising a VEGF in combination with TGF-β1 to enhance bone growth or formation. Contrary to Applicants' assertion, it is the combination of references that discloses the advantages of using an adenoviral vector to improve the expression of a gene of interest in a mammal, and the use of combinations of genes including a VEGF gene and TGF-β gene in stimulating bone growth. As discussed above TGF-β is merely an alternate name for TGF-β1 (as evidenced by the TGF-β1 entry in Online Mendelian Inheritance in Man, the OMIM database of Victor McKusick).

Allowable Subject Matter

Claims 11, 12, 32, 33, 42, 43, 46, 47, 54, 55, 60, 61, and 66-71 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your

questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER